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Risk Factors for Treatment Failure and Mortality Among Hospitalized Patients With Complicated Urinary Tract Infection: A Multicenter Retrospective Cohort Study (RESCUING Study Group)

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Background. Complicated urinary tract infections (cUTIs) are responsible for a major share of all antibiotic consumption in hospitals. We aim to describe risk factors for treatment failure and mortality among patients with cUTIs.

Methods. A multinational, multicentre retrospective cohort study, conducted in 20 countries in Europe and the Middle East. Data were collected from patients' files on hospitalised patients with a diagnosis of cUTI during 2013-2014. Primary outcome was treatment failure, secondary outcomes included 30 days all-cause mortality,among other outcomes. Multivariable analysis using a logistic model and the hospital as a random variable was performed to identify independent predictors for these outcomes.

Results. A total of 981 patients with cUTI were included. Treatment failure was observed in 26.6% (261/981), all cause 30-day mortality rate was 8.7% (85/976), most of these in patients with catheter related UTI (CaUTI). Risk factors for treatment failure in multivariable analysis were ICU admission (OR 5.07, 95% CI 3.18-8.07), septic shock (OR 1.92, 95% CI 0.93-3.98), corticosteroid treatment (OR 1.92, 95% CI 1.12-3.54), bedridden (OR 2.11, 95%CI 1.4-3.18), older age (OR 1.02, 95% CI 1.0071.03-), metastatic cancer (OR 2.89, 95% CI 1.46-5.73) and CaUTI (OR 1.48, 95% CI 1.04-2.11). Management variables, such as inappropriate empirical antibiotic treatment or days to starting antibiotics were not associated with treatment failure or 30-day mortality. More patients with pyelonephritis were given appropriate empirical antibiotic therapy than other CaUTI [110/171; 64.3% vs. 116/270; 43%, p <0.005], nevertheless, this afforded no advantage in treatment failure rates nor mortality in these patients.

Conclusions. In patients with cUTI we found no benefit of early appropriate empirical treatment on survival rates or other outcomes. Physicians might consider supportive treatment and watchful waiting in stable patients until the causative pathogen is defined.

Keywords. complicated urinary tract infection; pyelonephritis; risk factors; treatment failure; bacterial resistance.

Urinary tract infections (UTIs) are responsible for a major share of antibiotic consumption in hospitals [1, 2]. Complicated UTI (cUTI), as defined by the US Food and Drug Administration (FDA), applies to pyelonephritis or UTI in a host with predisposing conditions [3]. In patients with cUTI, infections are frequently caused by multidrug-resistant gram negative bacilli [4–7]. Bacterial resistance to antimicrobial agents has been identified in the European Union and many other countries as a major public health problem [8–11].

The presentation of patients with cUTI is changing over time while patients' characteristics are also changing: patients are older, with a high prevalence of comorbidities, instrumentation of the urinary tract, and polypharmacy, and with highly resistant pathogens [12, 13]; contemporary data are scarce.

We conducted a multicenter retrospective study looking for risk factors for treatment failure and a fatal outcome among hospitalized patients with cUTI. The study was performed in hospitals with a high incidence of cUTI caused by resistant pathogens, mainly extended-spectrum β-lactamase (ESBL)–carrying gram-negative bacteria. We focused on patients'

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characteristics, comorbidities, infection presentation, type of UTI, clinical management during hospitalization, and the impact of inappropriate empirical antibiotic treatment.

METHODS

Patients and Study Design

This is a multinational retrospective cohort study using patient charts for data collection. The study was conducted in Bulgaria (2 hospitals), Greece (2 hospitals), Hungary (3 hospitals), Israel (3 hospitals), Italy (3 hospitals), Romania (2 hospitals), Spain (3 hospitals), and Turkey (2 hospitals). We collected data on hospitalized patients who had a diagnosis of cUTI as the primary cause of hospitalization and patients hospitalized for another reason but who developed cUTI during their hospitalization, from 1 January 2013 to 31 December 2014. Patients were identified by searching for the appropriate *International Classification of Diseases, Ninth* or *Tenth Revision, Clinical Modification* codes [14, 15] at discharge on the hospital administration system [16]; inclusion and exclusion criteria were applied to these patients.

Inclusion criteria were patients with UTI and at least 1 of the following: indwelling urinary catheter, urinary retention, neurogenic bladder, obstructive uropathy, renal impairment caused by intrinsic renal disease, renal transplantation, urinary tract modifications, or pyelonephritis with normal urinary tract anatomy. UTI was defined in the presence of at least 1 of the following signs or symptoms: chills or rigors associated with fever or hypothermia, flank pain (pyelonephritis) or pelvic pain (cUTI), dysuria or urinary frequency/urgency, costovertebral angle tenderness on physical examination, *and* either urine culture with at least $\geq 10^5$ colony-forming units (CFU)/mL of a uropathogen (no more than 2 species) or at least 1 blood culture growing possible uropathogens (no more than 2 species) with no other evident site of infection. Only 1 episode per patient was included in the present analysis.

We retrieved demographic, bacteriological, and clinical data including baseline patient characteristics, comorbidities, place of acquisition of infection, predisposing risk factors, signs and symptoms of infection, laboratory and microbiological data, imaging test data, and infection management data including empirical antibiotic therapy, outcomes, details of discharge, readmission, and where applicable, date of death. The follow-up period was defined for up to 2 months after discharge. We used the following categories:

- UTI related to indwelling urinary catheterization, including long-term, short-term, and intermittent catheterization.
- Pyelonephritis: inflammation of the kidney tissue caused by bacterial infection in patients who have no other urinary tract modification, defined as sepsis, flank pain, or tenderness and no other urinary tract pathology.
- UTI related to anatomical urinary tract modification, including any urinary diversion procedure, nephrostomy or stents, or renal transplants.
- UTI related to obstructive uropathy, including any obstruction intrinsic or extrinsic to the urinary tract, such as stones, tumor, ureteral herniation, and prostate hyperplasia.
- UTI related to other events, including UTI that does not fulfill any other category.

Screening for ESBLs was defined as an isolate resistant to ceftazidime. If growth was detected in blood and urine, with different resistance patterns, blood cultures were given priority over urine cultures and screening for ESBL was defined by growth in blood cultures.

Our primary outcome was treatment failure, defined as any of the following conditions:

- Signs or symptoms of cUTI present at diagnosis that have not improved by day 5–7 of appropriate antibiotic therapy.
- New cUTI-related symptoms that have developed within 30 days of the original cUTI diagnosis.
- Urine culture taken within 30 days of the original cUTI diagnosis, either during or after completion of therapy, that grew $\geq 10^4$ CFU/mL of the original pathogen identified in the diagnostic sample.
- Death irrespective of cause within 30 days of the original cUTI diagnosis.

Thirty-day and 2-month mortality and adverse events were collected as secondary outcomes. Secondary outcomes, defined and analyzed only in patients alive at day 30, included time to clinical response, duration of antibiotic therapy, positive urine culture within 30 days, signs or symptoms not resolved by day 7, length of hospital stay, and readmissions to the hospital within 60 days of hospital discharge.

For data collection, an access-controlled, web-based electronic case report form was used. For confirmation of data quality, study sites were monitored and audited by a designated local third party.

Statistical Methods

We assumed a 20% treatment failure rate. A sample size of 1000 patients (approximately 40–60 patients per hospital) is sufficient to introduce 20 independent risk factors for treatment failure in a multivariable analysis. This assumption was calculated using the rule of 10 outcomes per 1 risk factor [17].

For univariate analysis, categorical variables were compared using χ^2 test or Fisher exact test, as appropriate. Normally distributed continuous variables were compared using *t* test, otherwise by Mann-Whitney *U* test. Normality of continuous variable was examined by the Kolmogorov-Smirnov test and by visual testing of quantile-quantile plots. The Breslow-Day test

was used to test for homogeneity of odds ratio (OR), to look for interactions of appropriate and inappropriate empirical treatment effect in subgroups with bacteremia and septic shock.

Multivariable analysis was performed to identify independent predictors for treatment failure and 30-day mortality. We used generalized estimating equation binary logistics to account for study site as a random-effects variable. Co-linearity was tested by a correlation matrix and variables with strong correlations (Spearman correlation coefficient >0.6) were omitted after clinical consideration. Missing data were handled by multiple imputations. The analysis was based on the assumption that the covariates were missing at random. Ten imputed data sets were created. All statistically significant covariates (Tables 1 and 3) were entered in the imputation model including variables that are predictive of the missing values [18].

The interaction of appropriate empirical treatment with the type of infection, Charlson score, functional capacity, and septic shock was tested; however, the interactions were not significant and were removed from the final model. For model fitting we used the quasi-likelihood under the independence model criterion. For each outcome (treatment failure and 30-day mortality) we tested 6 different models in order to fit the best model.

Statistical analysis was conducted using the IBM SPSS statistics 24 software. All reported *P* values are 2-sided and statistical significance was set at $P < .05$.

Table 1. Patient Characteristics for Treatment Failure

Characteristic	Entire Cohort (N = 981)	No Treatment Failure (n = 720)	Treatment Failure (n = 261)	*P* Value
Patient characteristics				
Sex (male)	449 (45.8)	136 (52.1)	313 (43.5)	.016
Age, y, median (IQR)	68 (56–80)	72 (59–83)	67 (55–78.75)	.000
Admission reason: other condition than UTI	351 (35.8)	133 (51)	128 (30.3)	.000
Place of residency: medical care facility	179 (18.2)	60 (23)	119 (16.5)	.021
Previous 30-d antibiotic treatment	189/980 (19.3)	46 (17.6)	143/719 (19.9)	.427
Functional capacity: bedridden	158 (16.2)	68 (26.2)	90 (12.5)	.000
Corticosteroid therapy	67 (6.8)	26 (10)	41 (5.7)	.019
Previous UTI infection within a year	239/980 (24.4)	63 (24.1)	176/719 (24.5)	.913
Acquisition site: hospital	194 (19.8)	76 (29.1)	118 (16.4)	.000
Comorbidities				
Charlson score, median (IQR)	2 (1–4)	3 (1–5)	2 (0–4)	.000
Dementia	134/980 (13.7)	43/260 (16.5)	91 (12.6)	.117
Chronic kidney disease	273 (27.8)	84 (32.2)	189 (26.3)	.067
Diabetes mellitus	263 (26.8)	70 (26.8)	193 (26.8)	.996
Metastatic cancer	48 (4.9)	23 (8.8)	25 (3.5)	.001
Cancer	176 (17.9)	65 (24.9)	111 (15.4)	.001
Infection presentation				
Septic shock (yes)	34/916 (3.7)	17/243)7)	17/672 (2.5)	.002
ICU admission	136 (13.9)	81 (31)	55 (7.6)	.000
Bacteremia	190 (19.4)	45 (17.2)	145 (20.1)	.310
Type of UTI infection				
Catheter associated	336 (34.3)	199 (27.6)	137 (52.5)	.000
Pyelonephritis	197 (20.1)	169 (23.5)	28 (10.7)	
Other	448 (45.7)	352 (48.9)	96 (36.8)	
Infection management				
Appropriate empirical treatment	429/806 (53.2)	97/211 (46)	332/595 (55.8)	.014
Days to antibiotic treatment start, median, (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	.006
UTI pathogen	n = 976	n = 259	n = 717	
Acinetobacter baumannii	27 (2.8)	18 (6.95)	9 (1.25)	.000
Pseudomonas aeruginosa	82 (8.4)	30 (11.6)	52 (7.3)	
Klebsiella pneumoniae	146 (15)	47 (18.1)	99 (13.8)	
Enterococcus spp	54 (5.5)	21 (8.1)	33 (4.6)	
Proteus mirabilis	73 (7.5)	26 (10)	47 (6.6)	
Escherichia coli	518 (53.1)	93 (35.9)	425 (59.3)	
Other	76 (7.8)	24 (9.3)	52 (7.3)	
Extended-spectrum β-lactamases	201 (20.5)	59 (22.6)	142 (19.7)	.323

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ICU, intensive care unit; IQR, interquartile range; UTI, urinary tract infection.

Table 2. Multivariable Analysis for Treatment Failure

Risk Factor	Multivariable Generalized Estimating Equation, OR (95% CI)	*P* Value
Metastatic cancer	2.89 (1.46–5.73)	.02
Septic shock	1.92 (.93–3.98)	.079
Infection source: indwelling catheter	1.48 (1.04–2.11)	.028
Appropriate treatment[a]	0.81 (.57–1.15)	.246
Duration of symptoms before hospitalization	0.99 (.97–1.02)	.656
Corticosteroid therapy	1.92 (1.12–3.54)	.018
Functional capacity: bedridden	2.11 (1.4–3.18)	.000
Age (per 1 y)	1.02 (1.007–1.03)	.001
ICU admission	5.07 (3.18–8.07)	.000

Hospital introduced as a random-effects variable, goodness of fit; quasi-likelihood under the independence model criterion = 966.74, constant β = –2.094.

Abbreviations: CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

[a]Antibiotic treatment matching the in vitro susceptibilities of the isolated pathogens in blood or urine.

Ethical Considerations

The study was approved by the local research ethics committee of each site. The processing of the personal data of patients was anonymized and complied with local data protection legislation and with the European Directive on the Privacy of Data (95/46/EC).

RESULTS

The demographic and clinical characteristics of the 981 included patients are shown in Table 1. The median age of the cohort was 68 years (interquartile range [IQR], 56–80 years); 45.8% (449/981) were male, 18.2% (179/981) came from medical care facilities, and 16.2% (158/981) were bedridden. Catheter-associated UTI (CaUTI) accounted for 34.4% (340/981) of infections, and 20% (197/981) were diagnosed as acute pyelonephritis.

Treatment Failure

Treatment failure was observed in 26.6% (261/981) of patients; 52.5% (137/261) in patients with CaUTI, 10.7% (28/261) in pyelonephritis, and 36.8% (96/261) in other UTIs (*P* = .001).

In univariate analysis, patients had higher failure rates if they were older, admitted for other conditions than UTI, bedridden, and with higher Charlson scores (Table 1). Patients who received early appropriate empirical antibiotic treatment had a lower risk of treatment failure compared with patients who did not receive appropriate empiric antibiotic treatment (46% [97/211] vs 55.8% [332/595]; *P* = .014). Bacteremia did not influence the risk for treatment failure; neither did pathogens positive on screening for ESBLs. *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were associated with higher failure rates and *Escherichia coli* associated with a lower rate.

In multivariable analysis for treatment failure, ICU admission (OR, 5.07; 95% confidence interval [CI], 3.18–8.07), septic shock (OR, 1.92; 95% CI, .93–3.98), corticosteroid treatment (OR, 1.92; 95% CI, 1.12–3.54), functional capacity (bedridden) (OR, 2.11; 95% CI, 1.4–3.18), older age (OR [increment of 1 year], 1.02; 95% CI, 1.007–1.03), metastatic cancer (OR, 2.89; 95% CI, 1.46–5.73), and CaUTI (OR, 1.48; 95% CI, 1.04–2.11) were found to be independent predictors of treatment failure (Table 2). When ICU is taken out of the model, septic shock becomes statistically significant (OR, 2.59; 95% CI, 1.24–5.39; *P* = .011). There was no strong correlation between these 2 parameters, and a model not taking ICU into account was inferior. Management variables, such as appropriate empirical antibiotic treatment or days to starting antibiotics, were not associated with treatment failure, nor were other comorbidities (Table 2).

Thirty-day Mortality

The all-cause 30-day mortality rate was 8.7% (85/976). Factors associated with 30-day mortality on univariate analysis are shown in Table 3.

Appropriate empirical antibiotic therapy did not influence 30-day mortality (36/69 [52.2%] vs 391/733 [53.3%]; *P* = .85); neither did pathogens positive on screening for ESBLs (12/85 [14%] in those who died vs 188/891 [21%] in those who did not; *P* = .128).

On multivariable analysis, risk factors for 30-day mortality were bedridden patients (OR, 2.22; 95% CI, 1.2–4.09), age (OR for 1 additional year of age, 1.05; 95% CI, 1.03–1.08), malignancy (OR, 2.55; 95% CI, 1.38–4.73), residency in a medical care facility (OR, 2.08; 95% CI, 1.12–3.86), patients admitted due to other condition (OR, 2.95; 95% CI, 1.55–5.61), presenting with septic shock (OR, 7.87; 95% CI, 3.19–19.37), and needing invasive mechanical ventilation (OR, 9.71; 95% CI, 4.46–21.1). Management variables, such as appropriate empirical antibiotic treatment or days to starting antibiotics, were not associated with 30-day mortality (Table 4).

UTI Subgroups

When differentiating patients by type of infection, treatment failure and 30-day mortality were higher in CaUTI than in pyelonephritis: 40% (137/336) vs 14.2% (28/197) and 15.9% (53/334) vs 2% (4/196), respectively. Twenty-seven percent of patients with pyelonephritis had bacteremia (54/198), compared to 19.7% with indwelling urinary catheters (67/340) and 15.7% (71/451) with other cUTI (*P* = .003). More patients with pyelonephritis were given appropriate empirical antibiotic therapy than other CaUTI (110/171 [64.3%] vs 116/270 [43%]; *P* < .005), but this did not improve treatment failure or mortality rates (Supplementary Table 1).

Secondary Outcomes

The time to clinical response was 3 days (IQR, 2–5 days), and did not differ between types of UTI. Median length of hospital stay was 7 days (IQR, 5–13 days), and was shorter in

Table 3. Risk Factors for 30-day Mortality

Characteristic	30-d Mortality (Yes) (n = 85)	30-d Mortality (No) (n = 891)	*P* Value
Patient characteristics			
Sex (male)	36 (42.2)	412 (46.2)	.49
Age, y, median (IQR)	79 (65–87)	67 (55–79)	.000
Admission reason: other condition	56 (65.9)	294 (33)	.000
Place of residency: medical care facility	30 (35.3)	147 (16.5)	.000
Previous 30-d antibiotic treatment	12 (14.1)	176 (19.8)	.207
Functional capacity: bedridden	33 (39.3)	122 (13.7)	.000
Corticosteroid therapy	9 (10.6)	58 (6.5)	.155
Previous UTI infection within a year	16 (18.8)	223/890 (25.1)	.202
Acquisition site: hospital	28 (32.9)	166 (18.6)	.002
Indwelling urinary catheter at admission	30 (35.3)	187 (21)	.002
Comorbidities			
Charlson score, median (IQR)	3 (2–6)	2 (0–4)	.000
Congestive heart failure	27 (31.8)	154 (17.3)	.001
Dementia	23 (27.1)	109 (12.2)	.000
Chronic kidney disease	30 (35.3)	241 (27)	.105
Chronic pulmonary disease	20 (23.5)	120 (13.5)	.011
Diabetes mellitus	23 (27.1)	238 (26.7)	.945
Metastatic cancer	11 (12.9)	37 (4.2)	.000
Active chemotherapy	6 (7.1)	24/890 (2.7)	.026
Cancer	27 (31.8)	149 (16.7)	.001
Renal impairment	29/83 (34.9)	218/891 (88.3)	.036
Infection presentation			
Septic shock (yes)	14 (17.3)	20 (2.4)	.000
ICU admission	33 (38.8)	103 (11.6)	.000
Invasive mechanical ventilation	32 (37.6)	62 (7)	.000
Type of UTI infection			
Catheter associated	53 (62.4)	281 (31.5)	.000
Pyelonephritis	4 (4.7)	192 (21.5)	
Other	28 (32.9)	418 (46.9)	
Infection management			
Appropriate empirical treatment[a]	36/69 (52.2)	391/733 (53.3)	.85
UTI pathogen			
Acinetobacter baumannii	5 (6)	20 (2.3)	.002
Pseudomonas aeruginosa	7 (8.3)	75 (8.5)	
Klebsiella pneumoniae	15 (17.9)	130 (14.7)	
Enterococcus spp	8 (9.5)	46 (5.2)	
Proteus mirabilis	13 (15.5)	60 (6.8)	
Escherichia coli	30 (35.7)	487 (54.9)	
Other	6 (7.1)	69 (7.8)	
Extended-spectrum β-lactamases	12 (14.1)	188 (21.1)	.128

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ICU, intensive care unit; IQR, interquartile range; UTI, urinary tract infection.

[a]Appropriate empirical treatment indicates antibiotic treatment matching the in vitro susceptibilities of the isolated pathogens in blood or urine.

pyelonephritis (6 days; IQR, 4–10 days) than in CaUTI (9 days; IQR, 5–17 days). Median duration of antibiotic therapy was 6 days (IQR, 4–10 days), and did not differ between types of UTI. Sixteen percent of the patients (156/966) were rehospitalized within 60 days (Table 5 and Supplementary Table 2).

DISCUSSION

Patients with complicated UTI had a treatment failure rate of 27% and a 30-day mortality rate of 9%, most of these due to CaUTI. Risk factors for treatment failure and 30-day mortality were older patients, bedridden and metastatic cancer patients, CaUTI as source of infection, and unstable patients presenting with septic shock or admitted to ICU for both outcomes. Higher body weight, coming from medical care facilities and admitted for a different reason than UTI, and need for mechanical ventilation were additional risk factors for 30-day mortality and corticosteroid therapy or treatment failure. Management variables, such as inappropriate empirical antibiotic treatment or days to starting antibiotics, were not associated with treatment failure or 30-day mortality.

Table 4. Multivariable Analysis for 30-day Mortality

Risk Factor	Multivariable Logistic Regression Analysis, OR (95% CI)	*P* Value
Septic shock	7.87 (3.19–19.37)	.000
Infection source		
Pyelonephritis	Reference category	
Other	2.4 (.85–6.73)	.096
Indwelling catheter	2.7 (.91–8.02)	.073
Place of residency: medical care facility	2.08 (1.12–3.86)	.020
Admission reason: other condition	2.95 (1.55–5.61)	.001
Weight (per 1 kg)	0.79 (.64–.99)	.037
Cancer	2.55 (1.38–4.73)	.003
Invasive mechanical ventilation	9.71 (4.46–21.1)	.000
Functional capacity: bedridden	2.22 (1.2–4.09)	.010
Age (per 1 y)	1.05 (1.03–1.08)	.000

Hospital introduced as a random-effects variable, goodness of fit; quasi-likelihood under the independence model criterion = 426.848, constant β = –.727.

Abbreviations: CI, confidence interval; OR, odds ratio.

We looked for the influence of appropriate empirical treatment in subgroups of very ill patients (patients with bacteremia or septic shock), but could not find a significant effect. Significantly more patients with pyelonephritis were given appropriate empirical antibiotic therapy than with CaUTI (64% vs 43%; $P < .005$); nevertheless, appropriate empirical antibiotic treatment afforded no advantage in treatment failure rates nor in 30-day mortality in these patients.

Regarding pathogens, *A. baumannii* and *P. aeruginosa* were associated with higher failure rates. The response of these pathogens to treatment might be slower, but we might not have captured all patient-associated risk factors for treatment failure, and these pathogens might reflect a different population of patients.

Few studies have been performed to define and characterize risk factors for treatment failure in cUTI and pyelonephritis.

Table 5. Secondary Outcomes

Outcome	No (%) of Episodes
In- hospital mortality	91/989 (9.2)
All-cause mortality within 30 d	85/976 (8.7)
All the other components of the composite primary outcome	
Positive urine culture within 30 d	72/984 (7.3)
Signs/symptoms not resolved by day 7	251/988 (25.4)
All-cause mortality for 2 mo after hospital discharge	36/989 (3.6)
Readmission to the hospital within 60 d of hospital discharge	156/966 (16.1)
Adverse events related to antibiotic treatment	73/986 (7.4)
Continuous variables	Median (IQR)
Time to clinical response	3 (2–5)
Length of hospital stay, d	7 (5–13)
Duration of antibiotic therapy, d	6 (4–10)

Abbreviation: IQR, interquartile range.

Pertel and Haverstock [19] retrospectively analyzed data on 522 adult patients from 2 prospective clinical trials designed to evaluate antibiotic regimens for urinary tract infections. Treatment failure rate was 15% overall; significant predictors for failure were hospitalization, the presence of resistant organism(s), diabetes mellitus, and a history of kidney stones. Failure rate was 53% for patients with at least 1 of these 4 risk factors. Patients in our study were all inpatients and therefore a different population. Efstathiou et al [20] retrospectively assessed 225 patients with cUTI and pyelonephritis and found recent hospitalization, previous use of antibiotics, and immunosuppression to be independent correlates for a resistant pathogen, which correlated with treatment failure. Additional predictors included nephrolithiasis in women and a history of recurrent UTI in men. None of these studies discussed management variables or empirical antibiotic treatment.

Reviewing the literature, the range of mortality rates in complicated UTI is very broad (2%–33%) [20–23], derived from the different compositions of included patients. In a recent study by Babich et al studying 315 hospitalized patients with CaUTI, mortality rate was 30.8% in a cohort consisting of old patients [24]. Lower mortality rate is seen in studies including strictly pyelonephritis and higher in studies including a more heterogeneous group of patients. All studies define their patients as cUTI or pyelonephritis but actually the inclusion criteria differ significantly, as do the outcomes, all raising doubt if these conditions should be combined in randomized controlled trials (RCTs) and emphasizing the need to separate these populations by explicit definitions. To note, the FDA and European Medicines Agency (EMA) differ in their recommended trial populations for cUTI RCTs. The FDA considers pyelonephritis an important subset of cUTI and states that approximately 30% or more of the clinical trial population should be patients with pyelonephritis for an indication for "treatment of complicated urinary tract infections including pyelonephritis [3]." EMA prefers that efficacy in acute pyelonephritis be studied separately and, if studied together, recommends stratification at enrollment and limiting the proportion with pyelonephritis.

The balance between preventing patients' deaths from sepsis and using antibiotics judiciously to prevent resistance development is largely determined by our belief in the benefit of appropriate empirical antibiotic treatment and the magnitude of the benefit [25]. Physicians try hard to treat patients with suspected infections with appropriate empirical therapy as soon as possible. This has a price of administering superfluous and unnecessary antibiotics, which has been proven to be associated with the rise of resistant pathogens, side effects, and no benefit for the individual patient and society [26].

Previous studies have found a significant association of early appropriate empirical treatment for bacteremia, sepsis, or septic shock with patient survival [27–30]. We found no impact of appropriate empirical treatment on treatment

failure or mortality. In a systematic review and meta-analysis of prospective studies, inappropriate empirical antibiotic treatment for sepsis was associated with a higher risk for a fatal outcome (OR, 1.6; 95% CI, 1.37–1.86) [29]. Most patients in these studies included all types of bacteremia and no study specifically applied to cUTI patients. UTIs are unique, especially in the CaUTI population, as it is often difficult to distinguish between symptomatic UTI and febrile illness from another source with asymptomatic bacteriuria, a very common finding. After 1 month of using a urinary catheter, almost 100% of patients will be colonized with bacteria [30]. Any febrile episode without a clear source in these patients might be regarded as CaUTI. Babich et al showed that appropriate empirical treatment did not change outcomes of long-term survival in patients with CaUTI (hazard ratio, 0.99; 95% CI, .75–1.3) [24].

Reisfeld et al examined the impact of appropriate empirical treatment on mortality among patients with cognitive decline and gram-negative bacteremia and found that appropriate empirical treatment was not associated with mortality benefit in the sickest subgroup of patients with decubitus ulcers [31]. The knowledge that appropriate empirical treatment is not associated with improved survival or treatment success among stable, non-ICU patients may allow holding back antibiotic therapy in these patients until better understanding the cause of fever and culture results.

Our study has several limitations: It is a retrospective study, in which each site enrolled 40–60 patients. Therapy decisions were taken by the attending physician, who managed patients according to local practice. Hospitals might differ in their threshold for admission, management, and coding of diagnoses. We tried to correct for this by using a strict and detailed protocol for collection of data; monitoring; and in the analysis by adding site as a random variable in our analysis. Another limitation might be overfitting of the model for mortality. We entered 10 variables into the model predicting 30-day demises in 85 patients. The strength of our study is the large sample size, the fact that it is multinational and multicenter, and our analysis by UTI subgroups and management variables that were not emphasized in previous publications.

Further research is needed in patients with cUTI, and especially in the group of patients with urinary catheters, to define the subgroup with a higher certainty of a UTI infection as the cause of fever (or other complaints) vs the group of patients with bacteriuria but fever of other origins, in which antibiotic treatment can be deferred. Septic shock emerged here (as in other studies) as an important determinant for treatment failure and a fatal outcome. Better management of septic shock is paramount; unfortunately, we have witnessed no major progress in the recent past. Further research is warranted to assess whether the response of different pathogens to treatment is truly different.

In conclusion, in a large cohort of patients with complicated UTIs, we found no benefit of early appropriate empirical treatment on survival rates or other outcomes. Physicians might consider supportive treatment and watchful waiting in stable patients until the cause of sepsis is clear and the causative pathogen is defined.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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